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Codon Selecti n in Y ast*

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Extreme codon bias is seen for the *Saccharomyces cerevisiae* genes for the fermentative alcohol dehydrogenase isozyme I (ADH-I) and glyceraldehyde-3-phosphate dehydrogenase. Over 96% of the 1004 amino acid residues analyzed by DNA sequencing are coded for by a select 25 of the 61 possible coding triplets. These preferred codons tend to be highly homologous to the anticodons of the major yeast isoacceptor tRNA species. Codons which necessitate side by side GC base pairs between the codons and the tRNA anticodons are always avoided whenever possible. Codons containing 100% G, C, A, U, GC, or AU are also avoided. This provides for approximately equivalent codon-anticodon binding energies for all preferred triplets. All sequenced yeast genes show a distinct preference for these same 25 codons. The degree of preference varies from greater than 90% for glyceraldehyde-3-phosphate dehydrogenase and ADH-I to less than 20% for iso-2 cytochrome *c*. The degree of bias for these 25 preferred triplets in each gene is correlated with the level of its mRNA in the cytoplasm. Genes which are strongly expressed are more biased than genes with a lower level of expression.

A similar phenomenon is observed in the codon preferences of highly expressed genes in *Escherichia coli*. High levels of gene expression are well correlated with high levels of codon bias toward 22 of the 61 coding triplets. As in yeast, these preferred codons are highly complementary to the major cellular isoacceptor tRNA species. In at least four cases (Ala, Arg, Leu, and Val), these preferred *E. coli* codons are incompatible with th preferred yeast codons.

Recent advances in nucleic acid analysis in general and in DNA cloning and sequencing in particular have made available a great deal of data on the primary structure of several viral, prokaryotic, and eukaryotic genes. The DNA or RNA from several mRNA-coding genes has been sequenced (compiled by Grantham and co-workers (1, 2)). The results obtain d agree well with the triplet codon: amino acid assignments which had been determined by indirect means (see (1966) *Cold Spring Harbor Symp. Quant. Biol.* 31.).

Most, if not all, mRNA-coding genes show a bias, sometimes subtle, but always statistically significant, in the choice of which of several degenerate triplets are used to code for a particular amino acid. Different genes exhibit different patterns of nonrandom codon usage, but different genes in the same genome frequently have related codon preference rules (2). A major difficulty in assessing which factor(s) is involved in selection by an organism of specific codon biases is the complex pattern of nonrandom codon utilization generally observed. Analyses by others suggest that no single, overriding selection process is responsible for the preferences in codon usage detected. This is not surprising since a variety of constraints beyond coding for a specific peptide may act on an mRNA sequence. The codon biases observed in a mature mRNA primary sequence may be a function of selective preferences acting on mRNA processing and transport, mRNA translation efficiency, and/or mRNA secondary structure and stability. In addition, specific triplet preferences may be a reflection of selective processes basically independent of mRNA structure and function, acting instead on the DNA sequence which the mRNA mirrors. These factors might include susceptibility of the DNA to mutagenic damage and cues for DNA replication, chromatin assembly, or even RNA polymerase promotion and termination (3, 4). To date, most of the models proposed for the basis of nonrandom codon usage have primarily involved various aspects of mRNA structure and translational efficiency (1, 2, 5–11).

Recent sequencing of the yeast genes coding for the very abundant proteins glyceraldehyde-3-phosphate dehydrogenase (12, 13) and alcohol dehydrogenase isozyme I (14) has disclosed three cases of codon selection far more strict than any yet seen. We have analyzed these sequences and compared them to the codon usage observed for several other sequenced genes from *Saccharomyces cerevisiae*. These data suggest that in bakers' yeast a common selective mechanism acts to heavily bias codon representation in the genes for ADH-I[1] and glyceraldehyde-3-phosphate dehydrogenase.

RESULTS AND DISCUSSION

Codon Usage in Six Yeast Genes—The published DNA sequence data for several yeast genes make it possible in each case to accurately determine both the amino acid sequence of the corresponding protein and the codon triplet used to code for each of its amino acids. Collation and summation of the codons used for each of seven yeast proteins yields the codon utilization summary in Table I. For two of these proteins, glyceraldehyde-3-phosphate dehydrogenase and alcohol dehydrogenase I, the usage of the 61 possible codon triplets is highly biased. For the two glyceraldehyde-3-phosphate dehydrogenase genes, only 29 codons are used and for ADH-I, only 33. In contrast with these two genes, those which code for yeast iso-1 and iso-2 cytochrome *c* employ 41 and 43 different codons, respectively.

The great similarities between the yeast glyceraldehyde-3-phosphate dehydrogenase and ADH-I genes both in the degree and direction of their codon preferences suggest that this

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[1] The abbreviation used is: ADH-I, alcohol dehydrogenase isozyme I.

usage pattern has functional significance and is not merely a statistical anomaly. Each one of the 28 codons *not* used in the ADH-I gene is also not used in either of the two genes coding for glyceraldehyde-3-phosphate dehydrogenase (Table I). It is evident, from the data in Table I and from more detailed comparisons made below, that codon usage for the yeast H2B1, H2B2, *CYC*1, and *CYC*7 genes is biased in this same direction, but to a lesser degree.

Most of the codon preferences manifested by the glyceraldehyde-3-phosphate dehydrogenase and ADH-I genes can be summarized by the following empirical rules.

1. For serine (UCN) and for four of the six amino acids which have 3- or 4-fold coding degeneracy ($XY\begin{matrix}U\\C\\A\\G\end{matrix}$), the codons XYC and XYU are used with roughly equal probability, whereas the codons XYA and XYG are never used. Serine, isoleucine, valine, threonine, and alanine follow this rule; proline and glycine do not.

2. For 2-fold degenerate codons with a pyrimidine in the wobble position, XYC is used and XYU is not used. This holds absolutely for phenylalanine, tyrosine, histidine, and asparagine, while aspartic acid has a 2-fold preference for C over U. This rule does not hold for cysteine as is discussed below.

3. For leucine (UUR), arginine (AGR), and for 2-fold degenerate codons with a purine in the third position, one of the alternative codons is used almost to the complete exclusion of the other. (UUG for Leu, AAG for Lys, CAA for Gln, GAA for Glu, and AGA for Arg).

4. For the two 4-fold degenerate amino acids (Gly, Pro) which do not obey the first rule, the predominant codon choices (CCA for Pro and GGU for Gly) are those which prevent the codon from being either 100% GC, 100% purine, or 100% pyrimidine.

Codon Usage versus Isoaccepting tRNA Abundance—A formal explanation for these empirical rules of codon preference can be found in the relative abundances of different isoaccepting yeast tRNAs and in their anticodon sequences. For each of the 16 amino acids whose tRNAs have been sequenced, the major isoaccepting species present in yeast is, in fact, that with an anticodon allowing it to translate the most frequently used codon (or $XY\begin{matrix}U\\C\end{matrix}$ codon pair) for that amino acid (Table II). Of the amino acids, including methionin and tryptophan, for which a single codon is used extensively or predominantly in glyceraldehyde-3-phosphate dehydrogenase and ADH-I, nine have a major tRNA whose anticodon is exactly complementary to that anticodon triplet. The two exceptions are glycine and cysteine. Thus, it would appear that when the major tRNA for an amino acid has as its wobble base either U, C, or G, there is selection for those codons in mRNA that can form a standard Watson-Crick base pair at the third position and against the alternative codon which would require wobble pairing. A different restriction in the use of wobble pairing (23) is seen for those major yeast tRNAs which have an inosine residue at anticodon position one (Table II, lines 1–4). Each of these corresponds to an amino acid coded both in glyceraldehyde-3-phosphate dehydrogenase and in ADH-I exclusively by pyrimidine-ended codons and never by the related purine-ended codons. This absolute correlation suggests that I-C and I-U base pairs are favored in codon-anticodon interaction and that I-A base pairs, although theoretically possible (23), may not actually occur. Consistent with this conclusion is the observation that none of the 11 yeast serine tRNA genes (24) which code for $tRNA^{Ser}_{2+1}$ (anticodon = IGA) have been found to be mutable to efficient ochre (UAA) suppressors (25). Further evidence for the absence of I-A base pairing is the existence in yeast of a separate UCA-decoding minor serine isoacceptor (26). UCG codons apparently are translated by yet another minor serine tRNA (26). In keeping with the paucity of these latter two tRNAs, UCA and UCG are not used to code for serine in yeast glyceraldehyde-3-phosphate dehydrogenase and ADH-I.

Codon-Anticodon Interactions—The two exceptions to the rule of strict complementarity between codon and anticodon of the major tRNA are cysteine (UG*U*)-anticodon *G*CA and glycine (GG*U*)-anticodon *G*CC. The choice of U rather than C in each of these cases may be explained by a strong avoidance of side by side GC base pairs in yeast codon-anticodon interactions (see below). With U having been chosen for codon position three, a G-U or I-U pair is made inevitable because A residues are never found in yeast tRNAs at the wobble base position. Adenosine residues specified for this position by the gene sequence are deaminated during tRNA maturation to form inosine residues. Therefore, the presence of U for position three in Cys and Gly codons precludes perfect complementarity because A at the corresponding anticodon position is unattainable.

Given the correlation noted between codons frequently used

TABLE I

Codon usage for eight yeast genes

The table lists the number of times each triplet appears in the plus strand of the DNA sequence coding for each of the following yeast proteins: 49, glyceraldehyde-3-phosphate dehydrogenase clone pgap491 (12, 13); 63, glyceraldehyde-3-phosphate dehydrogenase clone pgap63 (13); AD, alcohol dehydrogenase I (14); B1, histone H2B, gene H2B1 (15); B2, histone H2B, gene H2B2 (15); C1, iso-1-cytochrome *c* (16); C2, iso-2-cytochrome *c* (17).

	49	63	AD	B1	B2	C1	C2		49	63	AD	B1	B2	C1	C2		49	63	AD	B1	B2	C1	C2		49	63	AD	B1	B2	C1	C2
UUU	0	0	0	1	1	2	3	UCU	13	11	14	11	9	2	2	UAU	0	0	0	1	3	2	3	UGU	2	2	8	0	0	2	2
UUC	10	11	8	1	1	2	1	UCC	12	14	7	6	9	0	1	UAC	10	10	13	4	2	3	2	UGC	0	0	0	0	0	1	0
UUA	0	0	2	1	1	1	2	UCA	0	0	0	0	1	1	2																
UUG	21	20	19	5	5	5	3	UCG	0	0	0	0	0	1	0									UGG	3	3	5	0	0	1	1
CUU	0	0	0	0	0	1	0	CCU	0	1	2	1	1	1	3	CAU	0	0	1	1	1	2	3	CGU	0	0	0	0	0	0	0
CUC	0	0	0	0	0	0	0	CCC	0	0	1	0	0	0	0	CAC	8	8	10	1	1	2	0	CGC	0	0	0	0	0	0	0
CUA	0	1	3	0	0	1	0	CCA	12	10	10	4	4	3	2	CAA	5	6	9	4	3	2	0	CGA	0	0	0	0	0	0	0
CUG	0	0	0	0	0	0	0	CCG	0	0	0	0	0	0	0	CAG	0	0	0	0	1	0	3	CGG	0	0	0	0	0	0	0
AUU	9	7	9	3	4	2	3	ACU	12	10	5	9	6	3	1	AAU	0	0	0	0	0	2	1	AGU	0	0	0	0	0	0	2
AUC	11	12	12	5	4	2	1	ACC	12	13	9	2	3	3	1	AAC	12	14	11	3	3	5	6	AGC	0	0	0	1	0	0	0
AUA	0	0	0	0	0	0	1	ACA	0	0	0	1	2	2	3	AAA	1	2	4	7	8	6	9	AGA	11	11	8	6	5	3	2
AUG	6	7	7	1	1	3	3	ACG	0	0	0	0	0	0	4	AAG	25	24	20	13	11	10	8	AGG	0	0	0	0	1	0	1
GUU	22	23	19	4	5	1	1	GCU	26	23	19	12	10	3	4	GAU	8	7	2	2	2	1	4	GGU	25	24	41	4	4	8	8
GUC	15	12	17	1	2	0	1	GCC	6	10	16	4	7	4	1	GAC	17	13	14	1	1	3	1	GGC	0	0	3	0	0	2	1
GUA	0	0	0	0	0	0	1	GCA	0	0	0	1	0	0	2	GAA	14	15	20	8	7	5	3	GGA	0	0	0	0	0	0	3
GUG	0	0	0	0	0	2	0	GCG	0	0	0	1	0	0	1	GAG	0	0	0	0	1	2	3	GGG	0	0	0	0	0	2	0

TABLE II

Preferred codons in the ADH-I and glyceraldehyde-3-phosphate dehydrogenase (G3PDH) genes in relationship to anticodon sequences in the major yeast isoaccepting tRNAs

All nucleic acid sequences listed are written 5′-NNN-3′. The *underlined* nucleotides are those which base pair between anticodon position one and codon position three. Transfer RNA anticodon sequences are derived from the compilation of Gauss *et al.* (18). Determination of which of two or more isoaccepting tRNA species is the major one in yeast was done using the BD cellulose column chromatographic profiles of Gillam *et al.* (19) and the Sepharose 4B chromatographic experiments of Culbertson *et al.* (20). The major arginine isoacceptor, $tRNA^{Arg}_{UCU}$, was purified and sequenced by Kunzel and co-workers (21, 22). For $tRNA^{Phe}$, $tRNA^{Tyr}$, $tRNA^{Cys}$, and $tRNA^{Trp}$ only one isoaccepting species is known. G_m is 2′*O*-methylguanosine; Ψ is pseudouridine, C_m is 2′*O*-methylcytidine, and U* is believed to be a uridine derivative (18). The codon usage figures are the sum of the listed values for the two glyceraldehyde-3-phosphate dehydrogenase genes (12, 13) and ADH-I gene (14) given in Table I.

Amino acid	Major isoacceptor and its anticodon sequence	Preferred triplet(s) and the extent of their use in G3PDH + ADH-I	Use of all other triplets for that amino acid
Ala	$tRNA^{Ala}_{1}$ *IGC*	GC*U* (68), GC*C* (32)	0
Ser	$tRNA^{Ser}_{2}$ *IGA*	UC*U* (38), UC*C* (33)	0
Thr	$tRNA^{Thr}_{1a,1b}$ *IGU*	AC*U* (77), AC*C* (34)	0
Val	$tRNA^{Val}_{1}$ *IAC*	GU*U* (64), GU*C* (44)	0
Ile[a]	None sequenced	AU*U* (25), AU*C* (35)	0
Asp	$tRNA^{Asp}_{1}$ *GUC*	GA*C* (44)	17
Phe	$tRNA^{Phe}$ G_mAA	UU*C* (29)	0
Tyr	$tRNA^{Tyr}$ *GUA*	UA*C* (33)	0
Cys	$tRNA^{Cys}$ *GCA*	UG*U* (12)	0
Asn	None sequenced	AA*C* (37)	0
His	None sequenced	CA*C* (26)	1
Arg	$tRNA^{Arg}$ *U**CU	AG*A* (30)	0
Glu	$tRNA^{Glu}_{3}$ *UUC*	GA*A* (49)	0
Leu	$tRNA^{Leu}_{3}$ *CAA*	UU*G* (60)	6
Lys	$tRNA^{Lys}_{1}$ *CUU*	AA*G* (69)	7
Gly	$tRNA^{Gly}_{1}$ *GCC*	GG*U* (90)	3
Gln	None sequenced	CA*A* (20)	0
Pro	None sequenced	CC*A* (32)	4
Met	$tRNA^{Met}_{f,3}$ *CAU*	AU*G* (20)	
Trp	$tRNA^{Trp}$ C_mCA	UG*G* (11)	

[a] The most abundant isoleucine tRNA species in the yeast *Torulopsis utilis* has the anticodon 5′-*I*AU-3′ (18).

and tRNAs present most abundantly, there remains the question of why natural selection has favored these particular codons and tRNAs rather than others. Why, for example, are CGN arginine codons not used at all in either glyceraldehyde-3-phosphate dehydrogenase or ADH-I? This is but one manifestation of a general tendency not to use codons containing GC, CG, CC, or GG if this can be in any way avoided. The codons UCG, CCG, ACG, GCA, GCG, CGU, CGC, CGA, CGG, AGG, GGG, AGC, GGC, and CCC are totally absent from the mRNAs for ADH-I and glyceraldehyde-3-phosphate dehydrogenase. For each of these triplets, perfectly complementary codon-anticodon binding would entail side by side GC base pairs. This situation is always avoided, whenever possible, in the ADH-I and glyceraldehyde-3-phosphate dehydrogenase genes. Since only CCN triplets can code for proline, side by side GC base pairs are unavoidable. However, all yeast genes which have been sequenced contain primarily CCA (or CCU) proline codons (Table I) and avoid CCC and CCG triplets greater than 99% of the time. Although UCC serine, ACC threonine, and GCC alanine codons occur frequently in the ADH-I and glyceraldehyde-3-phosphate dehydrogenase genes, the presence of inosine as the wobble nucleotide in the tRNAs that recognize these codons (Table II) avoids the formation of side by side GC base pairs in the codon-anticodon interaction. A possible functional basis for the avoidance of side by side GC base pairs is contained in the analysis of codon-anticodon binding strength made by Grosjean *et al.* (27). These authors noted a tendency for different codon-anticodon pairs to have relatively similar binding constants. Higher binding constants than average would obtain if two GC base pairs were involved. Hence, the bias against GC, CG, CC, and GG-containing codons in yeast equalizes triplet-anticodon interactions by such codon choices as AGA (Arg) rather than CGN and GGU (Gly) rather than GGG or GGC. In other words, these and other similar codon choices which discriminate against side by side GC base pairs can have the effect of smoothing out the differences in codon-anticodon binding strength for different amino acids. Further examples of this "binding energy homeostasis" are evidenced by the predominant codon choices for leucine (UUG), tyrosin (UAC), lysine (AAG), and others which are made in such a way as to preclude codon-anticodon binding between sequences which are 100% A + U.

The results presented here suggest that the codons in the glyceraldehyde-3-phosphate dehydrogenase and ADH-I genes have evolved to produce optimal and uniform codon-anticodon binding energies with the most abundant isoacceptor tRNAs in the cell. Various other authors have discussed an expected relationship between tRNA availability (1, 7, 8, 11, 28, 29) and codon-anticodon interactions (6, 9) to explain nonrandom codon usage. Both phenomena seem to be involved for the glyceraldehyde-3-phosphate dehydrogenase and ADH-I genes. Independently of one another, these highly expressed genes have evolved coding sequences which optimize interaction with the most abundant tRNA molecules. Other types of selective pressures on codon usage must be less significant for these two yeast genes.

The results on yeast codon selection and the correlation with tRNA abundance and codon-anticodon binding efficiency presented here allow prediction of the anticodon sequences of various, as yet unsequenced, *S. cerevisiae*, tRNAs. For instance, the major $tRNA^{Ile}$ isoacceptor should have a 5′-IAU-3′ anticodon, the major $tRNA^{Pro}$ species should have a UGG (or *UGG) anticodon, and the most abundant $tRNA^{Gln}$ should have a UUG anticodon.

Codon Bias and mRNA Abundances—The data for the codon selection in ADH-I and glyceraldehyde-3-phosphate dehydrogenase point quite directly to a preferred set of 25 out of the 61 possible triplets. For 15 amino acids only one triplet is preferred, while for Thr, Ala, Ile, Val, and Ser either of two codons, one having a U and the other a C in the wobble position, is allowed. If we term these 25 codons the "preferred triplets," it is possible to measure the distance between any given mRNA sequence and the "preferred" mRNA sequence that could code for that particular protein. Table III presents such an analysis of codon bias for six sequenced mRNA-coding *S. cerevisiae* genes. The Codon Bias Index is a measure of the fraction of codon choices which is biased to 22 preferred triplets. A value of one indicates that for all of the triplets in the mRNA, only codons of the preferred variety are used. A value of zero indicates totally random choice. A Codon Bias Index significantly less than zero for a given gene indicates greater than random usage of the nonpreferred triplets. In calculating the Codon Bias Index for yeast proteins, we have excluded codons for methionine, tryptophan, and aspartic acid (the latter exhibits a degree of codon bias less than the 85% cutoff arbitrarily chosen to define a "preferred" triplet).

The observed values of the Codon Bias Index are very nearly 1.0 for both glyceraldehyde-3-phosphate dehydrogen-

TABLE III

The Codon Bias Index and approximate cellular mRNA levels for eight yeast genes

The Codon Bias Index is a fraction whose numerator is the total number of times that the preferred codons are used in the protein minus the number of such usages expected if the code were read randomly. The denominator is the total number of amino acid residues in the protein (excluding methionine, tryptophan, and aspartic acid residues) minus the random expectation for usage of the preferred codons. The latter quantity, which appears both in the numerator and denominator, is a sum of 17 products, each one being the number of residues in the protein of a given amino acid multiplied by the fraction of all codons for that amino acid in the genetic code dictionary which are "preferred" (1/6 for Leu and Arg; 2/3 for Ile; and 1/2 for Phe, *etc.*). The preferred codons were chosen as those that were used greater than 85% of the time in the ADH-I and glyceraldehyde-3-phosphate dehydrogenase (G3PDH) genes. By this criterion, only aspartic acid was disqualified as not having significant codon bias (GAC/GAU = 44/17). Data for Met and Trp are also not included as these amino acids have no degenerate codons. The ideal codons chosen were UUC, UUG, AUU, AUC, GUU, GUC, UCU, UCC, CCA, ACU, ACC, GCU, GCC, UAC, CAC, CAA, AAC, AAG, GAA, UGU, AGA, and GGU. The approximate cellular mRNA concentrations were determined by wheat germ translation for glyceraldehyde-3-phosphate dehydrogenase, ADH-I and enolase,[2] and iso-1 cytochrome *c* (30). The level of histone 2B mRNA was determined by L. Hereford.[3] The value for the iso-2 cytochrome *c* level was approximated by dividing the iso-1 cytochrome *c* mRNA level by 17. It is known that the ratio of iso-1 to iso-2 cytochrome *c* protein is about 17 to 1 (31). The codon biases of the two yeast enolase genes (peno 8 and peno 46) were calculated from the data of Holland *et al.* (32).

Gene	Codon Bias Index	Approximate % of total cellular mRNA
pgap 63 (G3PDH)	0.99	1.5–6
pgap 491 (G3PDH)	0.98	
peno 8	0.96	1–3
peno 46	0.93	
ADH-I	0.92	0.7–2
Histone 2B		
(H2B1)	0.75	0.4
(H2B2)	0.68	0.4
Iso-1 cytochrome *c*	0.50	0.05
iso-2 cytochrome *c*	0.15	0.003

ase genes and 0.92 for ADH-I, in keeping with the definitions of preferred triplets as those most used in these genes. For the two histone 2B genes, the values are significantly lower, and for the iso-1-cytochrome *c* gene, the codon bias is only 0.5. For iso-2-cytochrome *c*, the choice is nearly random as regards preferred *versus* nonpreferred triplets. In all cases where the intracellular level of mRNA or protein is known, this correlates well with the degree of codon bias (Table III). The most abundant protein (glyceraldehyde-3-phosphate dehydrogenase) is most biased, the least abundant protein is least biased, and the proteins of intermediate abundance fall into place as well.

Physiological Basis for Biased Codon Usage—Our analysis of codon usage for yeast nuclear genes has led to two major conclusions. First, the codon which is most frequently used to specify a given amino acid is, in nearly every case, exactly complementary to the anticodon sequence of the most abundant isoaccepting tRNA for that amino acid. Consequently, there is a limited set of codon triplets, 25 in all, which can be defined as "preferred codons." Second, for all yeast proteins, the preferred set is the same one. However, there is considerable variation in the extent to which any given protein uses only preferred codons or instead draws indiscriminately from the entire set of 61 sense codons. There is a remarkably strong correlation (Table III) between the extent of codon usage bias toward these 25 preferred codons and the level of a particular protein (and its mRNA) in yeast cells. Because a similar situation exists in *Escherichia coli* cells (see below), there would appear to be some general physiological reason why abundant proteins have biased codon usage and rare proteins do not.

The explanation which comes to mind most immediately involves the translation rate of mRNA for abundant proteins. Because these proteins are required at high intracellular levels (which we assume simply because they are abundant), it could be presumed that there is selective pressure to translate their mRNAs rapidly and repetitively. Because the concentration of charged cognate tRNA governs the step time required to add an amino acid opposite each codon, rapid translation is favored by the use of triplets for abundant tRNAs. Consequently, "synonymous" mutations from triplets for high abundance tRNAs to triplets for low abundance isoacceptors might be deleterious if they were to occur in genes for proteins required in high abundance. The continuing selection for a high output of that particular protein will act to retain a set of preferred codons within the gene. Conversely, for those proteins, such as iso-2-cytochrome *c*, which are not required in large amounts, speed of translation has little selective value. Consequently, synonymous mutations to triplets decoded by low abundance tRNAs would not be strongly selected against in the genes for these proteins and their pattern of codon usage would be more nearly random, as is the case.

Certain questions are raised by the hypothesis that evolutionary selection for a high rate of translation of highly expressed yeast genes is responsible for their bias toward codons which match the most abundant tRNA isoacceptors. Why couldn't the same high output of protein be achieved in other ways, by DNA changes which increase the rate of transcription, enhance the stability of mRNA, or augment the number of gene copies (13)? Optimization of each of these genetic parameters might equally well have served to provide a high output of gene product.

Another hypothesis to explain codon usage bias for highly expressed genes postulates a more pervasive deleterious effect, should codons corresponding to rare tRNA isoacceptors be used in mRNAs of high abundance. Consider what the effects would be if serine codon UCG, corresponding to a rare isoaccepting $tRNA^{Ser}$ (26), were used extensively in coding for an abundant yeast protein such as glyceraldehyde-3-phosphate dehydrogenase. Because of the low abundance of $tRNA^{Ser}_{UCG}$, the intracellular pool of aminoacylated $tRNA^{Ser}_{UCG}$ must be small relative to that for other tRNAs. When the hypothetical yeast strain grows on glucose medium, synthesizing large amounts of glyceraldehyde-3-phosphate dehydrogenase mRNA, translation of this RNA would draw heavily upon the pool of Ser-$tRNA^{Ser}_{UCG}$, discharging a large fraction of the molecules. Consequently, all yeast ribosomes at that moment translating mRNAs containing UCG codons could suffer a block in translation with consequent risk of early termination and/or translational error (33). Thus, the presence of UCG codons in highly expressed genes such as that for glyceraldehyde-3-phosphate dehydrogenase will have deleterious effects upon many intracellular targets. On an evolutionary time scale, these multiple effects could be eliminated by single base pair changes (UCG → UC^{U}_{C}) at third position site within the glyceraldehyde-3-phosphate dehydrogenase gene. On the other hand, the occasional usage of $tRNA^{Ser}_{UCG}$ by hundreds of genes making proteins of medium or low abundance (such as iso-1-cytochrome *c*) brings about little discharging of this rare isoaccepting tRNA. Consequently, there is no strong selective pressure against UCG

[2] J. Bennetzen, C. Denis, and E. T. Young, unpublished results.
[3] L. Hereford, personal communication.

codons in mRNAs coding f r this class of proteins. The example just given can be generalized as an explanati n for biased cod n usage for all amino acids having multipl isoaccepting tRNAs. The bias bserved f r phenylalanine (UUC), tyrosine (UAC), and cysteine (UGU) cod n usage has some other basis since only one tRNA species is present for each f these amino acids.

If the selective mechanisms we have proposed are partly or wholly responsible for the differences in codon usage between abundant and rare yeast proteins, this implies that effectively different genetic codes are operative for the two classes of proteins. A set of 20 tRNAs, efficiently recognizing 25 codons, translates nearly all of the coding sequences of the abundant yeast proteins. In addition to these major tRNAs, approximately 20 minor isoaccepting tRNAs are required for translation of minor yeast proteins. These yeast tRNAs are specialized for that function.

In proposing two different (and not mutually exclusive) physiological explanations for the observed pattern of yeast codon bias, we have assumed that a deviation from that pattern would result in lowered fitness for the yeast cell. This assumption can be tested and the nature of any deleterious effect identified by altering a highly expressed yeast gene *in vitro*, creating an inappropriate codon, and then reintroducing the mutated gene into yeast cells and testing them for physiological changes resulting from the mutation.

Comparison of Yeast Codon Usage to That in E. coli—The DNA sequences of the highly expressed *E. coli* genes *ompA* (34), *lpp* (35), *tufA* (36), and *tufB* (37) each exhibit a codon usage which is highly biased toward the same set of preferred codons, for five amino acids a completely different codon than that which codes for highly expressed yeast proteins (Table IV). The existence of codon bias for these proteins and for the less highly expressed ribosomal protein genes of *E. coli* has been noted previously (34, 35, 11, 38), as has a correlation between these codon usage patterns and the abundance distribution of 35 isoaccepting tRNAs in *E. coli* (11, 35, 38).

The set of preferred codons inferred from the codon usage data for the major *E. coli* outer membrane proteins *ompA* and lipoprotein and elongation factor TU (Table IV) can be used to calculate a codon bias index for other *E. coli* proteins (Table V), exactly as done above in Table III for yeast proteins. The results exhibit a striking correlation between the degree of codon bias and the cellular level of each *E. coli* protein, just as observed in yeast. These results indicate that the selective forces which cause greater codon bias for highly expressed genes have their effect both in yeast and in *E. coli*, although the maximum bias observed is lower in the bacterium.

TABLE IV

Codon usage summed for the highly expressed E. coli genes ompA (34), lpp (35), tufA (36), and tufB (37)

Preferred codon(s) in yeast	Amino acid	Preferred codon(s) in *E. coli* and use	Use of all other triplets for that amino acid
GCU, GCC	Ala	GCC not used; no clear preference	
UCU, UCC	Ser	UCU, UCC 27	7
ACU, ACC	Thr	ACU, ACC 53	4
GUU, GUC	Val	GUU, GUA 62	8
AUU, AUC	Ile	AUC 43	4
GAC	Asp	GAC 43	11
UUC	Phe	UUC 20	3
UAC	Tyr	UAC 25	3
UGU	Cys	No clear preference	
AAC	Asn	AAC 31	1
CAC	His	CAC 12	4
GAA	Glu	GAA 40	10
GGU	Gly	GGU, GGC 80	6
CAA	Gln	CAG 28	2
AAG	Lys	AAA 17	6
CCA	Pro	CCG 34	5
UUG	Leu	CUG 56	2
AGA	Arg	CGU 33	7

TABLE V

The Codon Bias Index and cellular protein levels for six E. coli genes

The amounts of ompA protein and lipoprotein were obtained from Dr. Masayori Inouye, S. U. N. Y., Stonybrook,[4] and the amounts of elongation factor TU and RNA polymerase β subunit from Dr. Patrick Dennis, University of British Columbia.[5] The amounts of single copy ribosomal proteins were calculated from the data given by Kjeldgaard and Gausing (41), using their values for glucose and casamino acid *E. coli* cultures to calculate the number of ribosomes per cell. L7/L12 was similarly calculated, but is present in four copies per ribosome. The amount of Lac repressor per *E. coli* cell is from Müller-Hill *et al.* (42).

E. coli protein	Codon bias index	Amount of the protein molecules per cell	Reference to codon usage
Major lipoprotein	0.84	750,000	(35)
Elongation factor TU			
tufA	0.84	[200,000–1 × 10^6]	(36)
tufB	0.81		(37)
ompA protein	0.78	200,000	(34)
Ribosomal proteins L7/L12	0.84	140,000–300,000	(11)
Other ribosomal proteins (present one each per ribosome)	0.61	35,000–75,000	(38)
RNA polymerase β subunit	0.53	7,000–15,000	(39)
Lac repressor	0.18	10	(40)

Effects of tRNA Isoacceptor Distribution upon the Efficiency of Gene Expression—In differentiated cells of higher organisms, changes in tRNA profiles have been observed to occur in a tissue-specific manner (29, 43, 44). To the extent that the resulting isoacceptor distribution matches the codon usage bias of abundant cell-specific mRNAs, the output of major proteins may be maximized and expression of minor RNAs maintained by mechanisms such as those discussed earlier.

The cloning of such a developmentally regulated higher organism gene and attempts to achieve its expression at a high level either in *E. coli* (45) or in yeast (46) are accompanied in effect by a dedifferentiation of the tRNA population to that which is characteristic of the host cell. It follows from the correlations which we and others (35, 36) have shown between abundant tRNAs and heavily used codons and from the differences in codon usage between *E. coli* and yeast (Table IV) that certain cloned genes may be more readily expressed in *E. coli* and others in yeast. For five amino acids (bottom of Table IV), the difference in biased codon usage between yeast and *E. coli* is very large indeed. For example, the codon AGA is used to code for 100% of the arginine residues in the most abundant yeast proteins (Table II), while in the three abundant *E. coli* proteins, CGU comprises 83% and CGC 17% of the arginine codon usage. Higher eukaryote mRNAs differ greatly from one another in arginine codon usage, with AG$\overset{A}{G}$ being preferred for valbumin, β globin, immunoglobulin (2), and interferon (47) mRNAs but CGN

[4] M. Inouye, personal communication.

[5] P. Dennis, personal communication.

codons preferentially used in histone mRNAs and mRNAs coding for several mammalian polypeptide hormones (2). These considerations suggest that highly efficient translation of cloned mammalian genes in microbial cells may require careful comparison of the codon usage of the gene in relationship to the codon preferences of each available host cell system. Certain genes may best be expressed in yeast, others in *E. coli*.

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